

Stochastic modeling of excitable dynamics: improved Langevin model for mesoscopic channel noise

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Abstract. Influence of mesoscopic channel noise on excitable dynamics of living cells became a hot subject within the last decade, and the traditional biophysical models of neuronal dynamics such as Hodgkin-Huxley model have been generalized to incorporate such effects. There still exists but a controversy on how to do it in a proper and computationally efficient way. Here we introduce an improved Langevin description of stochastic Hodgkin-Huxley dynamics with natural boundary conditions for gating variables. It consistently describes the channel noise variance in a good agreement with discrete state model. Moreover, we show by comparison with our improved Langevin model that two earlier Langevin models by Fox and Lu also work excellently starting from several hundreds of ion channels upon imposing numerically reflecting boundary conditions for gating variables.

Keywords: Excitable dynamics, ion channels, mesoscopic noise, Langevin description

1 Introduction

Hodgkin-Huxley (HH) model of neuronal excitability [1] provides a milestone for biophysical understanding of information processing in living systems [2] in terms of electrical spikes mediated by ionic currents through voltage-dependent membrane pores made by ion channel proteins. One considers the cell membrane as an insulator with specific electrical capacitance C_m per unit of area, which is perforated by ionic channels providing generally voltage-dependent parallel ionic pathways with specific conductances G_i per unit of area for various sorts of ion channels. This yields the following equation for transmembrane electrical potential difference V

$$C_m \frac{dV}{dt} + G_K(n)(V - E_K) + G_{Na}(m, h)(V - E_{Na}) + G_L(V - E_L) = I_{\text{ext}}. \quad (1)$$

Here, three ionic currents are taken into account, sodium Na, potassium K and unspecific leakage current (mainly due to chloride ions). This is nothing else

the Kirchhoff current law, which takes into account the ionic and capacitance currents, as well as an external current I_{ext} which can stimulate electrical excitations. This equation reflects assumption on Ohmic conductance of completely open ion channels with E_i being the reversal or Nernst potentials. They emerge due to the difference of ionic concentrations inside and outside of the excitable cell, which are kept approximately constant by the work of ionic pumps, which is not considered explicitly. Nonlinearity comes from the open-shut gating dynamics of sodium and potassium channels. The corresponding specific conductances

$$\begin{aligned} G_K(n) &= g_K^{\max} n^4(V, t), \\ G_{\text{Na}}(m, h) &= g_{\text{Na}}^{\max} m^3(V, t) h(V, t), \end{aligned} \quad (2)$$

depend on three voltage-dependent gating variables, n , m , and h , where $n(t)$ is the probability of one gate of potassium channel to be open (more precisely the fraction of open gates), m corresponds to one activation gate of sodium channel, and h is the fraction of closed sodium inactivation gates. One assumes four independent identical gates for potassium channel, hence its opening probability is n^4 , as well as three activation and one inactivation gate for the sodium channel. Hence, $m^3 h$ is the fraction of open sodium channels. The maximal conductances g_K^{\max} and g_{Na}^{\max} can be expressed via the unitary conductances $g_{i,0}$ of single ion channels as $g_i^{\max} = g_{i,0} \rho_i$, where ρ_i is the membrane density of the ion channels of sort i . The gating dynamics is in turn described by the relaxation kinetics

$$\frac{d}{dt}x = \alpha_x(V) (1 - x) - \beta_x(V) x, \quad x = m, h, n, \quad (3)$$

with voltage-dependent rates

$$\alpha_m(V) = \frac{0.1 (V + 40)}{1 - \exp[-(V + 40)/10]}, \quad \beta_m(V) = 4 \exp[-(V + 65)/18], \quad (4)$$

$$\alpha_h(V) = 0.07 \exp[-(V + 65)/20], \quad \beta_h(V) = \{1 + \exp[-(V + 35)/10]\}^{-1}, \quad (5)$$

$$\alpha_n(V) = \frac{0.01 (V + 55)}{1 - \exp[-(V + 55)/10]}, \quad \beta_n(V) = 0.125 \exp[-(V + 65)/80]. \quad (6)$$

Here the voltage is measured in millivolts and rates in inverse milliseconds. Other classical parameters of HH model suitable to describe excitable dynamics of squid giant axon are: $C_m = 1 \mu\text{F}/\text{cm}^2$, $E_{\text{Na}} = 50 \text{ mV}$, $E_K = -77 \text{ mV}$, $E_L = -54.4 \text{ mV}$, $G_L = 0.3 \text{ mS}/\text{cm}^2$, $g_K^{\max} = 36 \text{ mS}/\text{cm}^2$, $g_{\text{Na}}^{\max} = 120 \text{ mS}/\text{cm}^2$.

The set of four coupled nonlinear differential equations defined by (1)- (6) presents a milestone in biophysics and neuroscience because of its very clear and insightful physical background. In the same spirit, one can build up various other conductance-based biophysical models starting from the pertinent molecular background and following to the bottom-up approach. However, it assumes macroscopically large numbers of ion channels in neglecting completely the mesoscopic channel noise effects. The number of ion channels in any cell is, however, finite, and the corresponding channel noise can be substantial [2]. Especially, one confronts with this question by considering the spatial spike propagation among approximately piece-wise isopotential membrane clusters of ion channels [3].

2 Stochastic Hodgkin-Huxley equations

How to take stochastic dynamics of ion channels within the physical framework of HH model into account is subject of numerous studies [2,4,5]. The most rigorous way is to consider the variable population of open ion channels as a birth-and-death process [6]. Consider for simplicity a population of N independent two-state ion channels (one gate only) with opening rate α and closing rate β (constant under voltage clamp). Each ion channel fluctuates dichotomously between the closed state with zero conductance and the open state having unitary conductance g_0 . For such two-state Markovian channels, the stationary probability of opening is $p_0 = \alpha/(\alpha + \beta)$ and the averaged conductance is $\langle g(t) \rangle = p_0 g_0$. The number of open channels n is binomially distributed with probability $P_N^{\text{st}}(n) = p_0^n (1 - p_0)^{N-n} N!/(n!(N-n)!)$, average $\langle n \rangle = p_0 N$, and variance $\langle (n - \langle n \rangle)^2 \rangle = N p_0 (1 - p_0) = N \alpha \beta / (\alpha + \beta)^2$. For sufficiently large $N \geq 100$, we introduce quasi-continuous variable $0 \leq x(t) = n(t)/N \leq 1$, with smoothened binomial probability density $p_N^{\text{st}}(x) = N p^{xN} (1-p)^{N(1-x)} N! / (\Gamma(1+xN) \Gamma(1+(1-x)N))$. Use of approximate Stirling formula $n! \approx (n/e)^n$ yields

$$p_N^{\text{st}}(x) \approx C_N(\alpha, \beta) \left(\frac{\alpha}{x}\right)^{Nx} \left(\frac{\beta}{1-x}\right)^{N(1-x)}, \quad (7)$$

where $C_N(\alpha, \beta)$ is a normalization constant. We are looking for the best diffusional (continuous) approximation for discrete state birth-and-death process defined by the master equation

$$\dot{P}_N(n) = F(n-1)P_N(n-1) + B(n+1)P_N(n+1) - [F(n) + B(n)]P_N(n) \quad (8)$$

for $1 \leq n \leq N-1$, with forward rate $F(n) = \alpha(N-n)$ and backward rate $B(n) = \beta n$, complemented by the boundary conditions

$$\dot{P}_N(0) = B(1)P_N(1) - F(0)P_N(0), \quad (9)$$

$$\dot{P}_N(N) = F(N-1)P_N(N-1) - B(N)P_N(N). \quad (10)$$

2.1 Diffusional approximations for birth-and-death process

Kramers-Moyal expansion and standard diffusional approximation. A standard way to obtain diffusional approximation for $p_N(x) := P_N(xN)/\Delta x$ ($\Delta x = 1/N$) with rates $f(x) := F(xN)\Delta x$, $b(x) := B(xN)\Delta x$ is to do the Kramers-Moyal expansion [6,7], like $p_N(x + \Delta x) \approx p_N(x) + (\partial p_N(x)/\partial x)\Delta x + (\partial^2 p_N(x)/\partial x^2)(\Delta x)^2/2$, $f(x + \Delta x) \approx f(x) + (df(x)/dx)\Delta x + (d^2 f(x)/dx^2)(\Delta x)^2/2$, to the second order. This yields the Fokker-Planck equation

$$\frac{\partial}{\partial t} p(x, t) = -\frac{\partial}{\partial x} [f(x) - b(x)] p(x, t) + \frac{\partial^2}{\partial x^2} D_{\text{KM}}(x) p(x, t) \quad (11)$$

with diffusion coefficient $D_{\text{KM}}(x) = [f(x) + b(x)]/(2N)$. This Fokker-Planck equation corresponds to the Langevin equation

$$\dot{x} = f(x) - b(x) + \sqrt{2D_{\text{KM}}(x)} \xi(t), \quad (12)$$

where $\xi(t)$ is white Gaussian noise of unit intensity, $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$, in pre-point, or Ito interpretation [8]. This equation is quite general for any one-dimensional birth-and-death process within this standard diffusional approximation. For the considered population of ion channels,

$$\dot{x} = \alpha(1 - x) - \beta x + \sqrt{[\alpha(1 - x) + \beta x]/N} \xi(t). \quad (13)$$

This is stochastic equation for a gating variable in the stochastic generalization of Hodgkin-Huxley equations by Fox and Lu [5]. It replaces Eq. (3) with corresponding voltage-dependent $\alpha_x(V)$, $\beta_x(V)$, and $N = N_{\text{Na}} = \rho_{\text{Na}}S$ for m and h , or $N = N_K = \rho_K S$ for the variable n . S is the area of membrane patch, and $\rho_{\text{Na}} = 60 \mu\text{m}^{-2}$, $\rho_K = 18 \mu\text{m}^{-2}$ within HH model [4]. Clearly, in the limit $N \rightarrow \infty$ the channel noise vanishes, restoring the deterministic HH model. We name this model the second model by Fox and Lu (Fox-Lu 2) in application to stochastic HH dynamics.

Linear noise approximation. The further approximation (Fox-Lu 1 within stochastic HH model) is obtained by $D_{\text{KM}}(x) \rightarrow D_{\text{KM}}(x_{\text{eq}}) = \text{const}$, where x_{eq} is equilibrium point of deterministic dynamics, $f(x_{\text{eq}}) = b(x_{\text{eq}})$. It corresponds to the so-called $1/\Omega$ expansion with linear additive noise approximation advocated by van Kampen [6]. Then, with $x_{\text{eq}} = p_0 = \alpha/(\alpha + \beta)$ Eq. (13) reduces to

$$\dot{x} = \alpha(1 - x) - \beta x + \sqrt{2\alpha\beta/[N(\alpha + \beta)]} \xi(t). \quad (14)$$

Diffusional approximation with natural boundaries. The both diffusional approximations are not quite satisfactory because they do not guarantee the boundary conditions in a natural way. As a result, for a sufficiently small opening probability $p_0 \ll 1$, and not sufficiently large number of channels the negative values, $x < 0$, become possible with appreciable probabilities $p(x, t) > 0$. Likewise, the larger than one values, $x > 1$, are also possible when the opening probability p_0 is close to one. However, this deficiency can easily be corrected numerically by imposing reflecting boundary conditions at $x = 0$ and $x = 1$ in stochastic simulations. With this correction, Langevin approximation of stochastic HH dynamics is widely used [9,10,11,3]. However, it is not quite clear if this procedure indeed delivers the correct results [12]. To clarify the issue, we consider a different diffusional approximation with natural reflecting boundaries which naturally bound stochastic dynamics to the interval $0 \leq x \leq 1$.

For this, we first demand that the diffusional approximation is consistent with the stationary distribution of birth-and-death process, which can be expressed as $P_N^{\text{st}}(n) = \exp[-\Phi(n)]P_N^{\text{st}}(0)$ in terms of a pseudo-potential $\Phi(n) = -\sum_{i=1}^n \ln [F(i-1)/B(i)]$ [6]. Hence, in the continuous limit, $p_N^{\text{st}}(x) \propto \exp[-N\phi(x)]$, with pseudo-potential $\phi(x) = -\int_0^x \ln [f(x')/b(x')] dx' = \ln(1-x) - x \ln(\alpha(1-x)/(x\beta))$. This indeed yields the probability density (7). The corresponding Fokker-Planck equation must read

$$\frac{\partial}{\partial t} p(x, t) = \frac{\partial}{\partial x} \left(D(x) e^{-N\phi(x)} \frac{\partial}{\partial x} e^{N\phi(x)} p(x, t) \right) \quad (15)$$

$$= \frac{\partial}{\partial x} N D(x) \phi'_x(x) p(x, t) + \frac{\partial}{\partial x} D(x) \frac{\partial}{\partial x} p(x, t) \quad (16)$$

with

$$N D(x) \phi'_x(x) = b(x) - f(x) \quad (17)$$

in order to be also consistent with the deterministic limit $N \rightarrow \infty$. The last equation fixes the diffusion coefficient as

$$D(x) = \frac{1}{N} \frac{f(x) - b(x)}{\ln[f(x)/b(x)]} . \quad (18)$$

The Langevin equation which corresponds to this best diffusional approximation of the birth-and-death processes [7,13] reads

$$\dot{x} = f(x) - b(x) + \sqrt{2D(x)}\xi(t), \quad (19)$$

in the post-point, or Klimontovich-Hänggi interpretation [7]. In the standard Ito interpretation suitable for integration with stochastic Euler algorithm [8] the corresponding Langevin equation becomes

$$\dot{x} = f(x) - b(x) + D'_x(x) + \sqrt{2D(x)}\xi(t) \quad (20)$$

with spurious drift $D'_x(x)$. In application to stochastic dynamics of one gating variable it reads

$$\dot{x} = \alpha(1 - x) - \beta x + D'_x(x) + \sqrt{2D(x)}\xi(t) . \quad (21)$$

with

$$D(x) = \frac{1}{N} \frac{\alpha(1 - x) - \beta x}{\ln[\alpha(1 - x)/(\beta x)]} . \quad (22)$$

Replacing with such equations the stochastic equations for gating variables in the standard Langevin variant of stochastic Hodgkin-Huxley equations we obtain the improved Langevin description of mesoscopic channel noise, with natural boundaries because $D(0) = D(1) = 0$, i.e. the channel noise (and the probability flux) vanishes exactly at the reflecting boundaries, in the theory. Nevertheless, in numerical algorithm one must yet additionally secure such boundaries for any *finite* integration time step δt . Notice also that near the equilibrium point with $|f(x) - b(x)| \ll f(x) + b(x)$, $D(x) \approx D_{\text{KM}}(x)$, and the standard diffusional approximation is almost restored, almost, if to neglect the spurious drift correction $D'_x(x)$, which still remains within the Ito interpretation.

We test the best diffusional approximation for a gating variable against the earlier Langevin descriptions with reflecting boundary conditions implemented numerically. For this we use stochastic Euler algorithm with time step $\delta t = 0.001$ for several values of N and the simulation software XPPAUT [14]. The results are shown for $\alpha = 1$ and $\beta = 9$ with $p_0 = 0.1$ in Fig. 1 for $N = 100$ (a) and

$N = 10$ (b). As a big surprise, the simplest linear noise approximation actually seems to work best, if only to implement reflecting boundary conditions. For $N = 100$, it reproduces well the still somewhat skewed binomial distribution with the exact mean $\langle x \rangle = 0.1$ and standard deviation $\langle \Delta x^2 \rangle^{1/2} = 0.03$. Even for $N = 10$, it gives the mean closer to the correct value of 0.1 within the discrete state model. However, the variance then deviates from the theoretical value $\langle \Delta x^2 \rangle^{1/2} \approx 0.095$ larger than within two other approximations. For a sufficiently large $N = 1000$ (not shown), all three diffusional approximations give practically identical results, within the statistical errors of simulations. Surprisingly, all three work reasonably well even for $N = 10$! However, such a performance is *a priori* not guaranteed for stochastic nonlinear dynamics with voltage-dependent $\alpha(V(t))$ and $\beta(V(t))$. In fact, for a multistable dynamics the best diffusional approximation is generically expected [13] to operate essentially better.

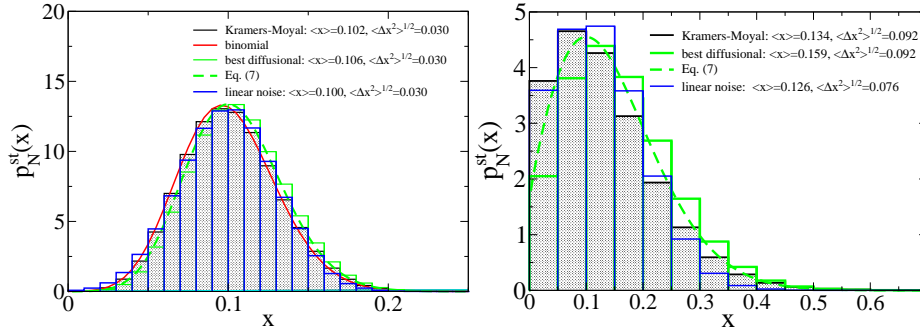


Fig. 1. Stationary distributions of gating variable x for two ensembles of ion channels with $\alpha = 1$ and $\beta = 9$, (a) $N = 100$ and (b) $N = 10$. Numerics are compared with binomial distribution (a) and distribution (7) for the best diffusional approximation

We compare three different Langevin descriptions of stochastic HH dynamics in Fig. 2, for two different membrane patches. Here, the interspike interval distributions are presented, together with the corresponding mean, $\langle \tau \rangle$, standard deviation, $\langle [\tau - \langle \tau \rangle]^2 \rangle^{1/2}$, and the relative standard variation, or the coefficient of variation, $C_V = \langle [\tau - \langle \tau \rangle]^2 \rangle^{1/2} / \langle \tau \rangle$, which measures the spike coherence. For $S = 10 \mu m^2$, all three approximations agree well. However, for $S = 1 \mu m^2$ the discrepancies become apparent, and we prefer our improved Langevin description on general theoretical grounds.

The coefficient of variation C_V , calculated within our Langevin variant of stochastic HH model, is plotted *vs.* the patch size S in Fig. 3. It displays a typical coherence resonance [15] behavior revealed earlier within stochastic HH models in [9,16] as a system-size coherence resonance. There exists an optimal patch size (optimal number of ion channels) with most coherent stochastic dynamics due to internal mesoscopic noise.

2.2 Summary and Conclusions

In this paper, we presented the best diffusional Langevin approximation for excitable cell dynamics within stochastic Hodgkin-Huxley model, with natural boundary conditions for the channel noise implemented. It has clear theoretical advantages over the standard diffusional approximation in the case of transitions induced by mesoscopic noise as discussed for bistable birth-and-death processes long time ago [13]. However, within stochastic HH model for a sufficiently large number of ion channels, the standard diffusional approximations were shown to work also very good. Hence, this work confirms the validity of the previous work done within the Langevin approximations of stochastic HH dynamics, for a sufficiently large number of channels. This does not mean, however, that for other excitable models the situation will not be changed. Generally, the improved Langevin description should operate better. Other stochastic models of excitable dynamics, e.g. stochastic Morris-Lecar model can easily be improved accordingly. This task, as well as comparison with discrete state stochastic models for channel noise, is left for a future investigation.

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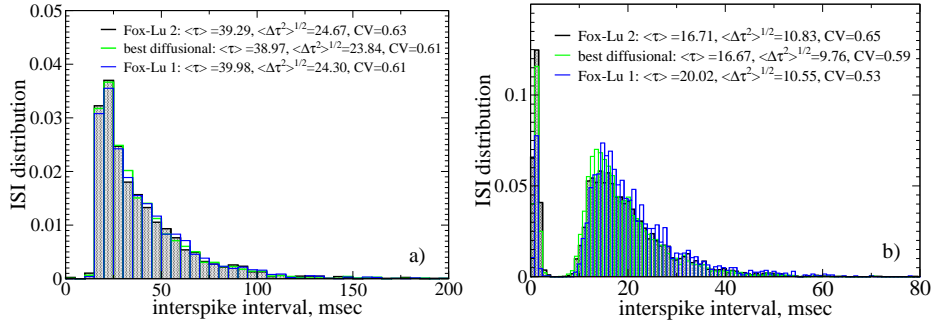


Fig. 2. Interspike time interval distribution for self-excitable dynamics, $I_{ext} = 0$, due to the channels noise for two membrane patches: (a) $S = 10 \mu m^2$ ($N_{Na} = 600$, $N_K = 180$), and (b) $S = 1 \mu m^2$ ($N_{Na} = 60$, $N_K = 18$).

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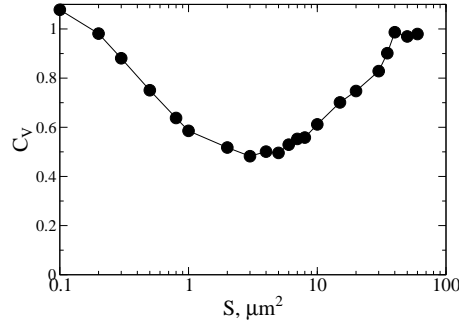


Fig. 3. Coefficient of variation versus the membrane patch size within our variant of stochastic HH model. Self-excitable dynamics, $I_{\text{ext}} = 0$.

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